Guidance for Industry
Photosafety Testing

DRAFT GUIDANCE

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Guidance for Industry

Photosafety Testing

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Guidance for Industry[1]
Guidance on Photosafety Testing

I. INTRODUCTION

This guidance is intended to help applicants decide whether they should test for photosensitivity and assess potential human risk for photochemical carcinogenesis (cancer) of their drug products during the clinical development process. The guidance describes a consistent, science-based approach for testing for topically and systemically administered drug products. Basic concepts of photobiology and phototesting are described, along with a process that can be used to make testing decisions or communicate risks.

Using the principles expressed in this guidance should prevent unnecessary testing while ensuring an adequate safety assessment for photochemical toxicity. The document does not recommend specific tests, but refers to some currently available testing methods. Sponsors may choose to use some of these tests to evaluate photosensitivity, photochemical carcinogenicity potential, or potential to enhance UV-associated skin carcinogenesis. Sponsors may propose alternative assays that are valid and scientifically sound. Alternative tests involving surrogate markers in the skin of humans receiving the drug product may clarify mechanisms of direct or indirect photoeffects seen in nonclinical studies (See Section IV, Development of Alternative Assays) and replace some nonclinical testing.

Photosafety testing (testing for adverse effects of drug products in the presence of light) is only recommended when it is felt that the results of testing would yield important safety information or be informative for the consumer and healthcare practitioner.

The glossary at the end of the document defines abbreviations and important terminology used to describe photobiologic concepts. Flow charts for evaluation of photosensitizing and nonphotosensitizing drug products are also provided at the end of the document. The flow charts illustrate the decision-making process, but do not address all situations that could arise during drug development.

[1] This guidance has been prepared by the Pharmacology Toxicology Coordinating Committee in the Center for Drug Evaluation and Research (CDER) at the Food and Drug Administration. This guidance represents the Agency's current thinking on issues related to photosafety testing. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public. An alternative approach may be used if such approach satisfies the requirements of the applicable statutes, regulations, or both.

II. BACKGROUND

A. Photosensitivity and Photococarcinogenicity

Photoirritation is a light-induced, nonimmunologic, skin response to a photoreactive chemical. The route of exposure to the photoreactive chemical may be by direct application to the skin or via the circulatory system following systemic administration. Phototoxic reactions resemble primary irritation reactions in that they may be elicited following a single exposure, in contrast to photoallergic reactions, which require an induction period prior to elicitation of the response. Examples of human photoirritating chemicals include the psoralens, tetracyclines, sulfonamides, phenothiazines, fluoroquinolones, dacarbazine, coal tar derivatives, and some nonsteroidal anti-inflammatory agents (Holzle et al., 1991; Johnson et al., 1997; *Physician's Desk Reference* 1998).

Photoallergy is an acquired, immunologically mediated reaction to a chemical initiated by the formation of photoproducts. The occurrence of a photoallergic response to a chemical is idiosyncratic (highly dependent upon the specific immune reactivity of the host). Two types of photoallergic responses are thought to occur. For both types, the chemical must absorb light. Then, the photosensitizer forms a photoproduct that is a more potent allergen than the parent compound (e.g., halogenated salicylanilide (Harber et al., 1980; Harber et al., 1982)) or binds to tissue proteins producing a complete antigen (e.g., sulfanilamide (Casteel 1991)). Compounds that elicit a photoirritation response also may be capable of initiating a photoallergic reaction[2]

Many diverse classes of drugs have been reported to be photosensitizers in the clinical setting (including antimicrobials, NSAIDs, antidepressants, anticonvulsants, diuretics, and antihypertensives) (Holzle et al., 1991; Johnson 1984; *Physician's Desk Reference* 1998). Acute photoirritation reactions can resemble sunburn and may range from a mild erythema to blistered skin with sloughing. Although a relatively small percentage of the population may show clinical symptoms of photosensitization, a much larger percentage may have immediate subclinical effects, with long-term consequences not apparent for many years. Nonclinical tests can identify some photosensitizing drug products before widespread clinical exposure occurs, allowing appropriate precautions to be implemented.

Data from animals and humans suggest that at least some photosensitizers enhance UV-associated skin carcinogenesis. An example is 8-methoxypsoralen (8-MOP) used in PUVA therapy. Several fluoroquinolones have been demonstrated to be photoirritants and photochemical carcinogens in hairless mice. However, data for many other classes of pharmaceuticals are unavailable. Many investigators believe that fluoroquinolone effects are mediated by reactive intermediates (Martinez et al., 1998) produced by UV-

[2] Examples of human photoallergens include promethazine, benzocaine, and *p*-aminobenzoic acid (Holzle et al., 1991, Johnson 1984).

activation, but the exact mechanism by which the fluoroquinolones exert photoirritation in animals and humans and photochemical carcinogenicity in animals is being studied.

It is believed that other compounds can enhance UV-induced skin carcinogenesis without being photoactivated. These include immunosuppressive agents (e.g., cyclosporin, *Physician's Desk Reference* 1998), and drug products that thin the protective layers of the epidermis (Pathak and Fitzpatrick 1983). Epidemiologic data (Abel 1989; Penn 1988) indicate that persons on chronic immunosuppressive therapy (e.g., cyclosporin following organ transplant) are at greater risk for skin cancer than the general population. Substances that thin the skin can enhance UV penetration, increasing the dose of UV that reaches responsive tissues. The minimal enythemal dose has been used to estimate UVB exposure in humans; however, it may not be the most sensitive measurement of UV damage. Pyrimidine dimer formation and P53 protein induction have been demonstrated in human skin in situ after suberythemal doses of solar-simulated light (Burren et al., 1998). Although the extent of changes in these parameters that are associated with human skin carcinogenesis are unknown, these parameters may be useful markers for enhanced UV exposure and potential damage to skin.

B. Photobiologic Principles

Photobiology is the study of the effect of optical radiation (UVA and/or UVB, visible, and IR) upon living systems (Smith 1989; Kochevar et al., 1993). The first law of photochemistry (Grotthaus-Draper Law) states that light must be absorbed for a photochemical event to occur (Megaw and Drake 1986). There is no photobiology without photochemistry. Photosensitization reactions (photoirritation and/or photoallergy) occur when the photoactive chemical enters the skin via dermal penetration or systemic circulation and becomes excited by appropriate UV or visible photons. A photoactive chemical may be the parent drug or excipient in a drug product or it may be a metabolite, impurity, or degradant.

Absorption of UV or visible photons by chemicals results in the promotion of electrons to higher energy states. These *excited-state molecules* (singlet or triplet state) possess the energy of activation required to react with macromolecules. Electrons in both excited singlet and triplet states can relax to the ground state either through transfer of energy to another molecule with emission of light, or through release of heat. *Excited state molecules* also may undergo photochemical changes such as *cis-trans* isomerization, fragmentation, ionization, rearrangement, and intermolecular reactions. The nature of a compound's excited state, the extent of intersystem crossing to reach the triplet state, and the types of possible photochemical reactions a compound can undergo determine the photosensitizing potential of a compound. The nonimmunologic photosensitivity response in a biologic system is directly related both to the light energy absorbed in the *action spectrum* and to the amount of compound (drug) present in the irradiated tissue. The environment of the chromophore, such as non UV-absorbing vehicles, may modify the photochemical response (Asker and Harris 1988).

Molecular characteristics of many photosensitizing agents include a relatively low molecular weight and a planar, tricyclic, or polycyclic configuration that is highly conjugated. Such characteristics result in more efficient production of excited singlet and triplet states after photoexcitation and may also increase the likelihood that a photoactivated compound will reach a target site and interact with a target. Key factors responsible for the photosensitivity reaction include (1) adequate concentration of a photoreactive chemical in the cutaneous circulation or distribution into the epidermis and (2) delivery of light energy of appropriate wavelength, duration, and intensity, and presence of molecular oxygen or other co-factors, if necessary (Casteel 1991).

The primary targets in a photosensitivity reaction include nucleic acids, proteins, and cellular and organelle membranes. Sensitizers have been reported to selectively accumulate in cell plasma membranes, for example, antracene and prophyrin (Ito 1978), cell nuclei such as psoralems (Pathak et al., 1974), lysosomes (Allison et al., 1966), and mitochondria (Sandberg and Romslo 1980; Salet and Moreno 1990; Selvaag et al., 1996). Four mechanisms through which absorption of light by a chromophore can result in a phototoxic response include the following:

1. A direct interaction of an excited molecule with cellular or molecular targets
2. Fragmentation or ionization of the excited molecule to an intermediate toxic photo product which then attacks the target
3. Generation of reactive oxygen species as a result of the reduction of the triplet state chromophore by an electron or hydrogen transfer from a compound in the environment (Type I photodynamic reaction)
4. The transfer of energy from the excited chromophore to oxygen, which generates a singlet oxygen species (a Type II photodynamic reaction)(Kornhauser et al., 1996)

Most compounds that evoke a photosensitization reaction are thought to act through a photodynamic mechanism. Psoralens can participate in either a direct acting or photodynamic mechanism (Pathak 1982). Direct reactions require close association or complex formation between the chromophore and the target before light absorption because the lifetime of an excited state is usually very short. Chlorpromazine is an example of a drug that forms a phototoxic intermediate after the absorption of light (Kochevar 1981; Schoonderwoerd et al., 1989).

UV-associated skin carcinogenesis can be enhanced by various mechanisms. In addition to photoactivation mechanisms, a compound may enhance UV carcinogenicity indirectly by altering biologic processes or optical or structural features of the skin. These indirect mechanisms of enhancement may include, but are not limited to, inhibiting repair mechanisms, altering the protective functions of the epidermis, or suppressing the immune system. Some emollients, which alter the optical properties of skin but are not photochemically active, have been demonstrated to accelerate UV-induced skin neoplasm development in mice (Jacobs et al., 1999).

Fortunately, the skin possesses protective barriers that minimize damage from light exposure. The skin is an optically heterogeneous medium that modifies the amount of radiation that may reach deeper dermal structures. Protective mechanisms include reflection, refraction, scattering, and absorption (Kornhauser et al., 1996). The stratum corneum reflects 5-10 percent of incident solar radiation. Intracellular components of stratum corneum cells also absorb or scatter most of the UVB (290-320 nm) radiation. Only 10-20 percent of incident solar radiation in the UVB band actually penetrates to the basal epidermal cell layer and superficial dermal vasculature of human skin. Electromagnetic radiation of wavelengths above 325 nm penetrates the epidermis to reach the deeper dermal layers. As much as 50 percent of incident UVA (320-400 nm) radiation may be transmitted to the basal epidermal cell layer and dermis. Excision-repair of UV-damaged DNA (Hessel et al., 1992; Kraemer et al., 1994; Lindahl et al., 1997) provides further protection against gene mutation and skin cancer.

C. Historical Approach to Photosafety Testing

Historically, the majority of systemically administered drugs have not undergone specific controlled testing for determining their potential for photosensitization. Topically applied, dermatologic drugs routinely have been tested for photosensitivity in both animals and humans if they absorb light in the UVA, UVB, or visible spectrum. In the absence of data from photosensitivity tests conducted in animals or humans, warnings about the potential for photosensitization generally have been added to labels after adverse reactions resulted during widespread clinical use of the products. Identification of photosensitivity effects before widespread human exposure is preferred, and animal studies have been useful to screen for photoeffects that may occur in humans.

Relatively few drug products have been tested to elucidate their potential for enhancing UV-mediated carcinogenic effects on the skin. By itself, UV light is a carcinogen in humans (IARC, 1992). The regulatory question is whether the drug increases the effect of UV light alone to such an extent that it possesses a significant increase in potential human carcinogenic risk such that the patient and the physician should be informed. Testing for photococarcinogenicity in humans, however, is impractical and unethical, and animal testing has thus been used as a surrogate. The method that has commonly been used for testing the potential photococarcinogenicity of a compound has been the Skh1-*hr* hairless mouse model. A positive response in this photococarcinogenicity assay is a decreased time to skin neoplasm development in animals exposed to the test material plus UV radiation (i.e., sunlight simulation) compared with exposure to the same dose of UV radiation alone. Information from this assay has been included in labels and may furnish a frame of reference for comparisons between drugs. Numerous researchers have conducted variants of this assay in several strains of shaved haired mice. However, because of the uncertainties involved in extrapolation from such animal testing to humans, development of alternative methods providing more relevant information for assessing the long-term adverse photoeffects of drug products relevant to humans would be desirable. When shown to be scientifically valid, such methods could be used for regulatory purposes. New, more focused, alternative methods may be especially useful when they can address specific mechanism-dependent phototoxicity concerns.

III. TESTING CONSIDERATIONS

A. Considerations for Testing a Drug Product or Drug Substance

For most drugs, it is generally acceptable to test only the drug substance for phototoxicity, without the excipients. The excipients usually have undergone independent testing, and a selective effect of excipients on the skin following systemic distribution is not anticipated. However, for topical products that will be applied to sun-exposed skin, the drug product, not just the active ingredient, should be evaluated. This is because many excipients in these types of products modify the skin, and dermal applications usually deliver relatively large amounts of both parent drug and vehicle to the skin. Many researchers have reported on the effects of topically applied vehicles on the skin, some of which alter the optical properties of human skin. Pharmaceutical vehicles (e.g., creams, gels, lotions or solutions) can decrease the amount of light reflected, scattered, or absorbed in the skin (Anderson and Parrish 1981; Serup et al., 1989), or increase the extent and/or depth of penetration in the skin of humans and mice (Marzulli and Maibach 1991; Baynes et al., 1996). Alternatively, vehicles can increase or decrease phototoxic properties (Kaidbey and Kligman 1974; Dearman et al., 1996) or photostability of drug products (Asker and Harris 1988; Islam and Asker 1995; Marti-Mestres et al., 1997). Vehicles may cause acanthosis, hyperkeratosis, and inflammation in rodent skin (Binder et al., 1997), change collagen gene expression in hairless mice (Chaquor et al., 1997), or influence the solubility and general stability of the drugs (Chellquist and Gorman 1992). Some cream-based vehicles have been found to be photosensitizers themselves (proprietary), while some oil-based emollients can increase UVB transmission and photococarcinogenicity in mice (Gibbs et al., 1985).

B. Testing for Photosensitivity (Photoirritation and Photoallergy)

1. Background

The intent of the procedures discussed below is to ascertain the potential of pharmaceuticals to elicit a photoirritation or a photoallergic reaction prior to widespread human use. The process described attempts to address these safety concerns adequately while optimizing the use of resources. To accomplish this goal, a decision tree approach is recommended that assesses both the need for testing and the type of testing that may be necessary. Alternative approaches may also accomplish this goal.

2. Proposed Approaches to Identifying Photosensitizers (Flow Chart A1)

Short-term photosensitivity testing in animals, perhaps followed by studies in humans, should be considered for all drug products that absorb UVB, UVA, or visible radiation (290-700 nm) and (1) are directly applied to the skin or eyes, or persist or accumulate in one of these areas, or (2) are known to affect the skin or eyes (see Flow Chart A1). A drug product would not be considered for testing for photosensitivity potential if the person receiving the drug would not be exposed to light in the sunlight spectrum while the drug or photoactive metabolites were in the body. Additionally, it would not be

necessary to conduct photosensitivity testing on a drug product that was applied only to skin not exposed to the sun if the drug did not undergo significant distribution to sun-exposed areas.

A description of the flow chart testing paradigm follows. Information regarding the ultraviolet/visible radiation absorption spectrum for the drug substance or drug formulation, as appropriate, is important in making a testing decision. A spectroscopic scan will determine if a drug absorbs within the 290-700 nm range of the electromagnetic spectrum. Although the scan is an important component of the safety assessment, presentation of only absorption maxima will not adequately address safety concerns. Drug products that do not absorb in this range (290-700 nm) will not be photoactivated (Box 1), and thus cannot be direct photosensitizers (Box 2). Some drugs elicit a photosensitivity reaction that is unrelated to the UV absorbance of the administered drug. These secondary mechanisms include perturbation of heme synthesis and increased formation of other light-absorbing endogenous molecules resulting from administration of nonlight-absorbing drugs. These effects may be identified from standard toxicology testing.

In addition to UV or visible absorption, the drug (or metabolites) should reach the skin or eye at levels sufficient to cause photosensitization reactions (Boxes 3 and 4). Tissue distribution studies of systemically administered drug products, usually included in IND submissions, can be used to assess the extent of partitioning into the skin or eyes. In the absence of partitioning into light exposed compartments, photosensitivity testing is unlikely to be informative and need not be conducted. Agents used for photodynamic therapy, however, may be an exception, and valuable safety information may be generated even if partitioning into the skin or eyes does not occur.

When drugs are identified as photosensitizers, they currently carry a warning to avoid sun exposure; this practice should continue (Box 6). In the absence of human data, a drug shown to be a photoirritant in nonclinical studies could be indicated as potentially causing photosensitivity. When adequate human data addressing photosensitivity are available, they would be included in the description of the product and would supplant animal data. Adverse event reports in humans can directly serve as a basis for warning about for photosensitivity.

3. Testing of Reformulations (Flow Chart A2)

Although it is important to consider excipients in testing for phototoxicity, it is not necessary to test most reformulations of a topical product for nonclinical photoeffects. Excipient changes that could have significantly different effects on the skin relevant to phototoxicity, however, should be tested. For example, a switch to a cream formulation from an acetone solution of a new, uncharacterized, drug substance should generally be evaluated for photoeffects. Information on the phototoxicologic properties of excipients and their effects on the penetration of the drug substance into the skin is useful in further defining the need to study new formulations. Inclusion of topical excipients not

previously studied for phototoxic effects in a new formulation could also warrant testing of the new formulation.

4. Tests for Evaluation of Photosensitivity

A number of methods and approaches currently are in use that test for photosensitivity. Animal models (generally mice or guinea pigs, but also rabbits or swine) have been discussed by Marzulli and Maibach (1996) and Lambert et al. (1996). Several in vitro screens for photoirritation, such as the 3T3 NRU phototoxicity test, are being evaluated (Spielmann et al., 1998). Data from such studies may provide sufficient information when conditions of the study are appropriate for the evaluation of the drug product of interest and, in any case, may be important in planning more comprehensive in vivo assessments. For in vivo nonclinical studies, acute drug exposure followed by simulated sunlight exposure is generally considered adequate to identify potential risks. Assessments may be incorporated into ongoing general toxicity studies in some circumstances. Human studies are also often conducted to follow up on potential risks identified based on animal or in vitro evaluations. We encourage the submission of specific data that may help in evaluating the regulatory acceptance of such assays.

IV. TESTING FOR ENHANCEMENT OF UV-ASSOCIATED SKIN CARCINOGENESIS (DIRECT PHOTOCHEMICAL CARCINOGENICITY OR INDIRECT EFFECTS IN SKIN)

A. Considerations and Decision Tree for Testing Photosensitizing Drugs for Long-Term Photosafety

The philosophy behind the guidance that follows is that long-term photosafety testing should be conducted only when it can provide useful information. Long-term studies should be avoided when sufficient information has already been collected for a drug or a class of drugs to appropriately inform potential users regarding photoreactivity.

Once a systemically or dermally administered drug has been identified as a photosensitizer in animal or human testing (see Flow Chart A1), one should consider the drug's potential to increase UV-associated skin cancer risk (Flow Charts B and C). Because patients are already cautioned against excessive sunlight exposure during use of photosensitizing drugs, sponsors could choose to strengthen these warnings with regard to photocarcinogenic potential, rather than conduct testing to determine the photochemical carcinogenicity potential for photosensitizing drugs. The option to strengthen the warning statements without conducting additional testing would be appropriate primarily in those circumstances where photochemical carcinogenic activity would not affect approvability or significantly reduce the utility of a drug product. The warning statement should convey the basis of the warning and the conditions under which the potential carcinogenic effect is likely to be realized (for example, see Box 2, Flow Chart B).

Warnings alone may be sufficient because drug products that are photosensitizers cause rapid erythema (sunburn) reactions in patients who expose themselves to sun without adequate protection. Unlike many drug side effects, sunburn is immediately apparent to patients, who become quickly aware of the reactions during use. Other circumstances for which product warning statements, rather than testing, may be appropriate include the following:

- Drugs having structures significantly similar to known photochemical carcinogens
- Drugs that are in a known pharmacologic class of photochemical carcinogens where the pharmacology of the product is believed to be directly related to the carcinogenic potential
- Drugs for which several other tests for photoreactivity, such as in vitro photogenotoxicity, adduct formation, human phototoxicity, or shorter-term in vivo nonclinical tests are positive
- Drugs that have been identified in other assays that do not include UV sunlight, such as traditional two-year bioassays or transgenic assays as carcinogens with potential human relevance
- Drugs for indications intended for populations in which the life expectancy is short (i.e., less than five years)

The warning should be informative, advising patients to avoid being in the sun, or, if sunlight exposure can not be avoided, to use protective clothing and broad-spectrum (UVA/UVB) sunscreens (when the wavelengths eliciting photosensitivity are in the range covered by the sunscreen). It should be recognized, however, that subclinical photosensitivity responses with prolonged use could also result in increased skin cancer risk. In general, for the above cases, warning statements are considered an adequate option, and phototesting, although potentially scientifically informative, is not considered warranted. In those cases where phototoxicity testing may be of value, it may often be conducted in phase 4 of the drug development process (i.e., post-approval).

For drugs where the approvability or utility would be an issue, testing beyond that noted above may be appropriate. Testing should be conducted using a model for which there is evidence that relevant endpoints are assessed and considered scientifically valid (Box 4). In some circumstances, a drug sponsor may want to demonstrate that, despite initial results suggesting a potential for photocarcinogenicity, the drug does not pose a risk for UV-associated skin cancer. The results of appropriately conducted assays along with evidence of, for example photosensitivity, would be included in the evaluation of potential risk and any communication of the overall phototoxic risk (Boxes 5 and 6).

Developing and evaluating short-term assays that predict the potential of chemicals to increase the UV-associated human skin cancer risk would be extremely helpful. Short-

term assays that measure photoreactivity (such as photogenotoxicity) have been developed in the hope that they would provide information about the potential to enhance UV-induced skin carcinogenesis. The interpretation of such assays, however, is not always straightforward, and their role in the evaluation of human risk should be assessed. Although the most widely performed test for the potential to enhance UV-induced skin cancer is the hairless albino mouse model with solar simulation, a test that takes approximately 12 months to complete, other tests can also be considered for regulatory purposes. Tests that are felt by the scientific community to be the best available assays for predicting long-term human effects should be used. Thus, scientifically valid alternative assays for evaluating the photochemical carcinogenicity potential are appropriate. When considering testing strategy, we encourage sponsors to discuss issues with the appropriate CDER review staff. One potential strategy is the use of surrogate markers in human skin to evaluate the consequences of combined drug and UV exposure. Use of surrogates should be considered and supported based on a thorough evaluation of the scientific data (see Section IV, Development of Alternative Assays).

B. Decision Tree for Testing Nonphotosensitizing Drugs for Long-Term Photosafety

This approach would apply to products used chronically. As noted earlier, drug products that do not cause photosensitivity reactions may enhance UV carcinogenicity. The possible association of nonphotosensitizers with increased risk of skin cancer is less obvious than for photosensitizing drugs and is thus much more difficult to recognize, predict, and evaluate. Patients using a nonphotosensitizing product that enhances UV carcinogenicity may not have an indication, such as sunburn or sun sensitivity, that they have increased their risk of skin cancer. In such cases, patients may make no effort to change their habits and avoid sunlight, thus further increasing their risk. The decision tree used for nonphotosensitizers attempts to balance the risks associated with these potentially *silent* enhancers of UV-induced skin carcinogenesis, while attempting to identify areas where testing is unnecessary. Pharmacologic activity (e.g., immunosuppression or alteration of the protective function within the epidermis) (see below) could provide information on such risks. It is anticipated that, even in the absence of information about such risks, most nonphototoxic drugs would not be tested for potential to enhance UV-induced skin carcinogenesis, even if they are administered chronically. This assumes that when administered chronically, drugs usually will be tested for carcinogenicity in a traditional chronic study (see Flow Chart C).

The approach for nonphotosensitizing drugs is described as follows:

1. Conditions of use

Nonphotosensitizing drugs that are not used chronically do not appear to present a significant risk of enhancing UV-induced skin carcinogenesis. Thus, it is highly unlikely that they should be tested in any assay for potential to enhance UV-induced skin cancer. (Chronic use may be either continuous or substantial repeated use and may justify such

testing.) In addition, drug products intended solely for use in populations with a short life expectancy (less than five years) need not be tested.

2. Dermal drug consideration (Box 3)

In general, topically applied drugs for which the intended effect is localized only to the area of application to non-sun-exposed skin and which do not reach pharmacologically measurable systemic levels will not need to be tested for potential to enhance UV-induced skin cancer. This also applies to other drugs that do not reach measurable systemic levels.

3. Reasons to suspect drug may enhance UV-induced skin carcinogenesis (Box 5)

The majority of drug products that are investigated and marketed are not photosensitizers and are unlikely to be photococarcinogens. However, a major class of known human photococarcinogens (e.g., immunosuppressants such as cyclosporin (Abel, 1989; Penn, 1988)) are nonphotosensitizing. In addition to appearing at internal sites, neoplasms appear relatively rapidly in the skin of immunosuppressed patients, particularly in areas exposed to sunlight. There are other examples of nonphotosensitizing drugs that enhance UV-induced skin carcinogenesis in mice (Jacobs et al., 1999). The mechanisms of enhancement by these nonphotosensitizing drugs or vehicles have not been studied and can only be surmised. Some of the mechanisms by which nonphotosensitizing vehicles or drugs may enhance UV-induced skin carcinogenesis include, but are not limited to, immunosuppression, neoplastic promotion, inhibition of apoptosis or DNA repair, irritation, altering the protective layers of the epidermis or changing the optical properties of the skin. Such mechanisms are applicable to both rodent and human skin and are biologically plausible mechanisms of enhancement. A product that changes the optical properties of the skin (some emollients) or alters the protective layers of the epidermis can greatly change UV penetration of the skin or the effective UV dose that the skin receives. The literature contains ample references to the effects of vehicles on skin and on the overall performance of a drug product. These and other indirect effects (discussed in the Development of Alternative Assays, Section IV, and above) can also occur in human skin and may be as important as direct photoreactive effects. For example, in studies sponsored by the cosmetics industry, increased sensitivity to UVB by persons using alpha-hydroxy acid preparations was suggested. As a consequence, the Cosmetic Ingredient Review Expert Panel (CIR 1997) recommended that persons using these products avoid unprotected exposure to the sun. The alpha-hydroxy acids used in these studies do not absorb UV between 280 and 700 nm. Thus, a thoughtful approach is called for when deciding if additional testing for potential to enhance UV-induced skin carcinogenesis is justified.

4. Warning or test *(Boxes # 6, 7, 8)*

If preliminary evaluations suggest that a drug or drug product may have the potential to enhance UV-induced skin carcinogenesis, the sponsor should either warn of this potential effect or conduct studies to evaluate this potential. Such studies could be a panel of

appropriately selected and scientifically valid surrogate markers in human skin, referred to in Section IV, Development of Alternative Assays.

C. Development of Alternative Assays

Mouse skin and human skin share many of the same responses to sunlight and drugs. Exposure to sunlight clearly modifies DNA and causes nonmelanoma skin cancer in both animals and humans (IARC, 1992). Although there are a number of differences, many of the proposed mechanisms by which drug substances or drug products may enhance UV-associated skin carcinogenesis are shared by mice and humans. Alternative assays for evaluating the potential to indirectly enhance UV carcinogenicity may be appropriate, provided that they are scientifically supported. A testing strategy can be discussed with the appropriate CDER staff. Identification of appropriate surrogate markers in human skin for increased UV exposure or UV damage is encouraged, and commentary on specific alternative methods is sought to improve testing procedures.

Alternative tests may provide information on the relevance of, or sensitivity to, adverse photoeffects in vitro or in animals relative to humans, and could replace currently used tests when sufficiently scientifically supported. Alternative tests to be investigated could include, but would not be limited to, in vitro measures of photocytotoxicity (e.g., the 3T3 assay), in vitro measures of photogenotoxicity (e.g., in Salmonella, yeast, or V79 cells), and transgenic models or surrogate markers (molecular, biochemical, cellular, or structural) for enhancement of UV-induced skin carcinogenesis in human skin. The minimal erythemal dose, sunburn cell number, P53 alterations, dimer formation in DNA, and other endpoints have been proposed as markers of increased UVB exposure or skin damage, but development of other scientifically valid assays is encouraged. Markers for UVA exposure, as well as for UVB exposure, would be desirable. Although the preferred radiation exposure in these assays would be sunlight simulation, at a minimum, the appropriate absorption spectrum for a photoreactive drug product should be covered. Assays assessing immunosuppression, inhibition of DNA repair or apoptosis, particularly in human skin, would also be useful. Strengths and limitations of the various assays are important to know. Correlation of the in vitro results for photoirritation with data from controlled clinical studies would add to the potential utility of such tests. Correlation of surrogates in animal skin with the surrogates in human skin for the same UV dose could provide a basis for evaluation (data-based) of the size of a response in a clinical surrogate that would translate into a clinically meaningful increase in skin cancer risk. When submitting comments on this draft guidance to the docket, please include any information that would support the evaluation of alternative tests, both in vitro and in vivo, human and nonhuman assays. Such data would be especially useful during the finalization of this guidance.

REFERENCES

Abel, E. A., 1989, "Cutaneous Manifestations of Immunosuppression in Organ Transplant Recipients," *J. Am. Acad. Dermatol*. 21 (2 part 1): 167-179.

Allison, A. C., I. A. Magnus, and M. R. Young, 1996, "Role of Lysosomes and of Cell Membranes in Photosensitization," *Nature* 209: 874-878.

Anderson, R. R., and J. A. Parrish, 1981, "The Optics of Human Skin," *J. Invest. Dermatol.* 77: 13-19.

Asker, A. F., and C. W. Harris, 1988, "Influence of Certain Additives on the Photostability of Physostigmine Sulfate Solutions," *Drug Development and Industrial Pharmacy* 14 (5): 733-746.

Baynes, R. E., C. Browne, H. Freeman, and J. E. Riviere, 1996, "In Vitro Percutaneous Absorption of Benzidine in Complex Mechanistically Defined Chemical Mixtures," *Toxicol. Appl. Pharmacol.* 141: 497-506.

Binder, R. L., J. Firriolo, L. C. Totman, E. I. Goldenthal, J. F. Nash, and A. L. Kraus, 1997, "Influence of Vehicle on Skin Response to Benzoyl Peroxide (BPO) in F344 Rats and B6C3F1 Mice," Abstract # 955, the 37th Annual Meeting of the Society of Toxicology.

Burren, R., C. Scaletta, E. Frenk, R.G. Panizzon, and L.A. Applegate, 1998, "Sunlight and Carcinogenesis: Expression of p53 and Pyrimidine Dimers in Human Skin Following UVA I, UV I +II and Solar Simulating Radiations," *Int. J. Cancer* 76: 201-206.

Casteel, S. W., 1991, "Cutaneous Photosensitization," *Dermal and Ocular Toxicology: Fundamentals and Methods*, D.W. Hobson, Ed., CRC Press, Boca Raton, FL pp. 193-220.

Chaquor, B., G. Bellon, S. Seite, J. P. Borel, and A. Fourtanier, 1997, "All Trans-Retinoic Acid Enhances Collagen Gene Expression in Irradiated and Non-Irradiated Hairless Mouse Skin," *J. Photochem. Photobiol. B: Biology* 37: 52-59.

Chellquist, E. M., and W.G. Gorman, 1992, "Benzoyl Peroxide Solubility and Stability in Hydric Solvents," *Pharm. Res. 9* (10): 1341-6.

CIR (Cosmetic Ingredient Review), 1997, *Safety Assessment of Glycolic Acid, Ammonium, Calcium, Potassium, and Sodium Glycolate, Methyl, Ethyl, Propyl, and Butyl Glycolate, and Lactic Acid, Ammonium, Calcium, Potassium, Sodium, and TEA- Lactate, Methyl, Ethyl, Isopropyl, and Butyl Lactate, and Lauryl, Myristyl, and Cetyl Lactate*, Final Report of the Cosmetic Ingredient Review Expert Panel, June 6, 1997.

Dearman, R. J., M. Cumberbatch, J. Hilton, H. M. Clowes, I. Fielding, J. R. Heylings, and I. Kimber, 1996, "Influence of Dibutyl Phthalate on Dermal Sensitization to Fluorescein Isothiocyanate," *Fundam. Appl. Pharmacol.* 33: 24-30.

Gibbs, N. K., A. R. Young, and I. A. Magnus, 1985, "Failure of UVR Dose Reciprocity for Skin Tumorigenesis in Hairless Mice Treated with 8-Methoxypsoralen," *Photochem. Photobiol.* 42 (1): 39-42.

Harber, L. C., I. E. Kochevar, and A. R. Shalita, 1980, *Photomedicine*, Plenum Press: New York.

Harber, L. C., R. B. Armstrong, and M. Ichikawa, 1982, "Current Status of Predictive Animal Models for Drug Photoallergy and Their Correlation with Drug Photoallergy in Humans," *J. Natl. Cancer Inst.* 69: 237-244.

Hessel, A., R. J. Siegle, D.L. Mitchell, and J. E. Cleaver, 1992, "Xeroderma Pigmentosum Variant with Multisystem Involvement," *Arch. Dermatol.* 128 (9): 1233-1237.

Holzle, E., N. Neumann, B. Hausen, B. Przybilla, S. Schauder, H. Honigsmann, A. Bircher, and G. Plewig, 1991, "Photopatch Testing: The 5 Year Experience of the German, Austrian, and Swiss Photopatch Test Group," *J. Am. Acad. Dermatol.* 25: 59-68.

IARC, 1992, "Solar and Ultraviolet Radiation," *IARC Monographs on the Evaluation of Carcinogenic Risk to Humans,"* Vol. 55, IARC, WHO.

Islam, M. S. and A. F. Asker, 1995, "Photoprotection of Daunorubicin Hydrochloride with Sodium Sulfite," *PDA J. Pharmaceut. Sci. Technol.* 49 (3): 122-126.

Ito, T., 1978, "Cellular and Subcellular Mechanisms of Photodynamic Action: The 1O2 Hypothesis as a Driving Force in Recent Research," *Photochem. Photobiol.* 28: 493-508.

Jacobs, A., J. Avalos, P. Brown, and J. Wilkin, 1999, "Does Photosensitivity Predict Photocarcocarcinogenicity?" *Internat. J. Toxicol*. 187 (4): 191-198.

Johnson, B. E., N. K. Gibbs, and J. Ferguson, 1997, "Quinolone Antibiotic with Potential to Photosensitize Skin Tumorigensis," *J. Photochem. Photobiol. B: Biology* 37: 171-173.

Johnson, B. E., 1984, "Light Sensitivity Associated with Drugs and Chemicals," *Physiol. Pathophysiol. Skin* 8: 2542-2606.

Kaidbey, K., and A. Kligman, 1974, "Topical Photosensitizers: Influence of Vehicles on Penetration," *Arch. Dermatol.* 110: 868-870.

Kochevar, I. E., 1981, "Phototoxicity Mechanisms: Chlorpromazine Photosensitized Damage to DNA and Cell Membranes," *J. Invest. Dermatol*. 77: 59-64.

Kochevar, I. E., M.A. Pathak and J. A. Parrish, 1993, "Photophysics, Photochemistry, and Photobiology," *Dermatology in General Medicine,* Fitzpatrick, T. B., A. Z. Eisen, K. Wolff, I. M. Freedburg, K.F. Austen, Eds,. Fourth ed., McGraw-Hill, New York, pp. 1627-1638.

Kornhauser, A., W. G. Wamer, and L. A. Lambert, 1996, "Cellular and Molecular Events Following Ultraviolet Irradiation of Skin," In *Dermatotoxicology*, Fifth ed., Taylor and Francis, Washington, DC.

Kraemer, K. H., M. M. Lee, A.D. Andrews, and W.C. Lambert, 1994, "The Role of Sunlight and DNA Repair in Melanoma and Nonmelanoma Skin Cancer -- The Xeroderma Pigmentosum Paradigm," *Arch. Dermatol.* 130 (8): 1018-1021.

Lambert, L. A., W. G. Wamer, and A. Kornhauser, 1996, "Animal Models for Phototoxicity Testing," in *Dermatotoxicology*, Fifth ed., Marzulli, F. N., and H. I. Maibach, eds., Taylor and Francis, New York. pp. 515-529.

Lindahl, T., P. Karran, and R. D. Wood, 1997, "DNA Excision Repair Pathways," *Curr. Opin. Genet. Dev.* 7(2): 158-169.

Marti-Mestres, G., G. Fernandez, N. Parsotam, F. Nielloud, J. P. Mestres and H. Maillols, 1997, "Stability of UV Filters in Different Vehicles: Solvents and Emulsions, Drug Development Industry," *Pharmacy* 23 (7): 647-655.

Martinez, L. J., R. H. Sik, and C. F. Chignell, 1997, "Fluoroquinolone Antimicrobials: Singlet Oxygen, Superoxide and Phototoxicity," *Photochem. Photobiol.* 67 (4): 399-403.

Marzulli, F. N., and H. I. Maibach, 1991, *Dermatotoxicology*, Fourth ed., Marzulli, F. N., and H. I. Maibach, eds., Taylor and Francis, New York, p. 585.

Marzulli, F. N., and H. I. Maibach, 1996, *Dermatotoxicology*, Fifth ed., Marzulli, F. N., and H. I. Maibach, eds., Taylor and Francis, New York, p. 231-237.

Megaw, J. M. and L. A. Drake, 1986, *Photobiology of the Skin and Eye*, Marcel Dekker: New York.

Pathak, M. A. and T. B. Fitzpatrick, 1974, *Sunlight and Man*, T. B. Fitzpatrick, Ed., Tokyo, U. of Tokyo Press, pp. 725-750.

Pathak, M. A., D. M. Kramer, and T. B. Fitzpatrick, 1974, "Photobiology and Photochemistry of Furocoumarins (psoralens)," *Sunlight and Man*, Fitzpatrick, T. B., Ed., University of Tokyo Press, Tokyo.

Pathak, M. A. 1982, "Molecular Aspects of Drug Photosensitivity with Special Emphasis on Psoralen Photosensitization Reaction," *J. Natl. Cancer Inst*. 69: 163-170.

Penn, I., 1988, "Tumors of the Immune Compromised Patient," *Ann. Rev. Med*. 39: 63-73.

Physicians Desk Reference, 1998, 52nd ed., Medical Economics Co., Montvale, NJ.

Salet, C. and G. Moreno, 1990, "Photosensitization of Mitochondria. Molecular and Cellular Aspects," *J. Photochem. Photobiol. B Biol.* 5: 133-150.

Sandberg, S. and I. Romslo, 1980, "Porphyrin-sensitized Photodynamic Damage of Isolated Rat Liver Mitochondria," *Biochim. Biophys. Acta* 593(2): 187-95.

Schoonderwoerd, S. A., G. M. J. Beijersbergen van Henegouwen, and S. van Belkum, 1989, "In Vivo Photodegradation of Chlorpromazine," *Photochem. Photobiol*. 50 (5): 659-664.

Selvaag, E., H. Anholt, J. Moan, and P. Thune, 1996, "Phototoxicity Due to Sulphonamide Derived Oral Antidiabetics and Diuretics: Investigations in a Cell Culture Model," *Photodermatol. Photoimmunol. Photomed*. 12(1): 1-6.

Serup, J., A. Winther and C. Blichmann, 1989, "A Simple Method for the Study of Scale Pattern and Effects of a Moisterizer--Qualitative and Quantitative Evaluation by D-Squame Tape

Compared with Parameters of Epidermal Hydration," *Clin. Experimental Dermatol*. 14: 277-282.

Smith, K. C., Ed., 1989, *The Science of Photobiology*, 2nd ed., Plenum Press: New York.

Spielmann, H., M. Balls, J. Dupuis, W. J. Pape, G. Pechovitch, et al., 1998, "The International EU/COLIPA in Vitro Phototoxicity Validation Study: Results of Phase II (Blind Trial): Part 1: The 3T3 NRU Phototoxicity Test," *Toxicology in Vitro* 12 (3): 305-327.

GLOSSARY

ADR: Adverse drug reaction

IR: Infrared radiation 0.76 µm- 1000 µm

MED: Minimal erythema dose

8-MOP: 8-Methoxypsoralen

NSAID: Nonsteroidal anti-inflammatory drug

Indirect photoeffects: Effects of an agent, vehicle, or product on the optical, structural, molecular, or physiologic properties of the skin, such that the interaction of light and skin or effects of drug in skin are altered.

Photoallergy: An acquired, immunologically mediated reaction to a drug or chemical initiated by the formation of photoproducts when that drug or chemical is exposed to light

Photochemical carcinogenesis: Carcinogenesis resulting from a reaction with photoactivated drug

Photococarcinogenicity: The direct (photochemical carcinogenesis) or indirect enhancement of UV-associated skin carcinogenesis (e.g., sunlight-associated carcinogenesis) by a drug or chemical

Photoirritation: A light-induced, nonimmunologic, skin response to a photoreactive drug or chemical

Photoproducts: Compounds resulting from a reaction between a drug or chemical and radiation

Photosafety testing: Testing for the potential of a drug product to cause photoirritation or photoallergy or to enhance UV-induced skin carcinogenesis

Photosensitivity: A photoirritation- or photoallergy-induced reaction

Photosensitizer: A drug product that causes an adverse effect in the presence of UVA/UVB or visible light

Phototoxicity: A light-induced, nonimmunologic, response to a photoreactive drug or chemical

PUVA: Psoralen plus UVA treatment

UV: Ultraviolet radiation (wavelengths below 400 nm)

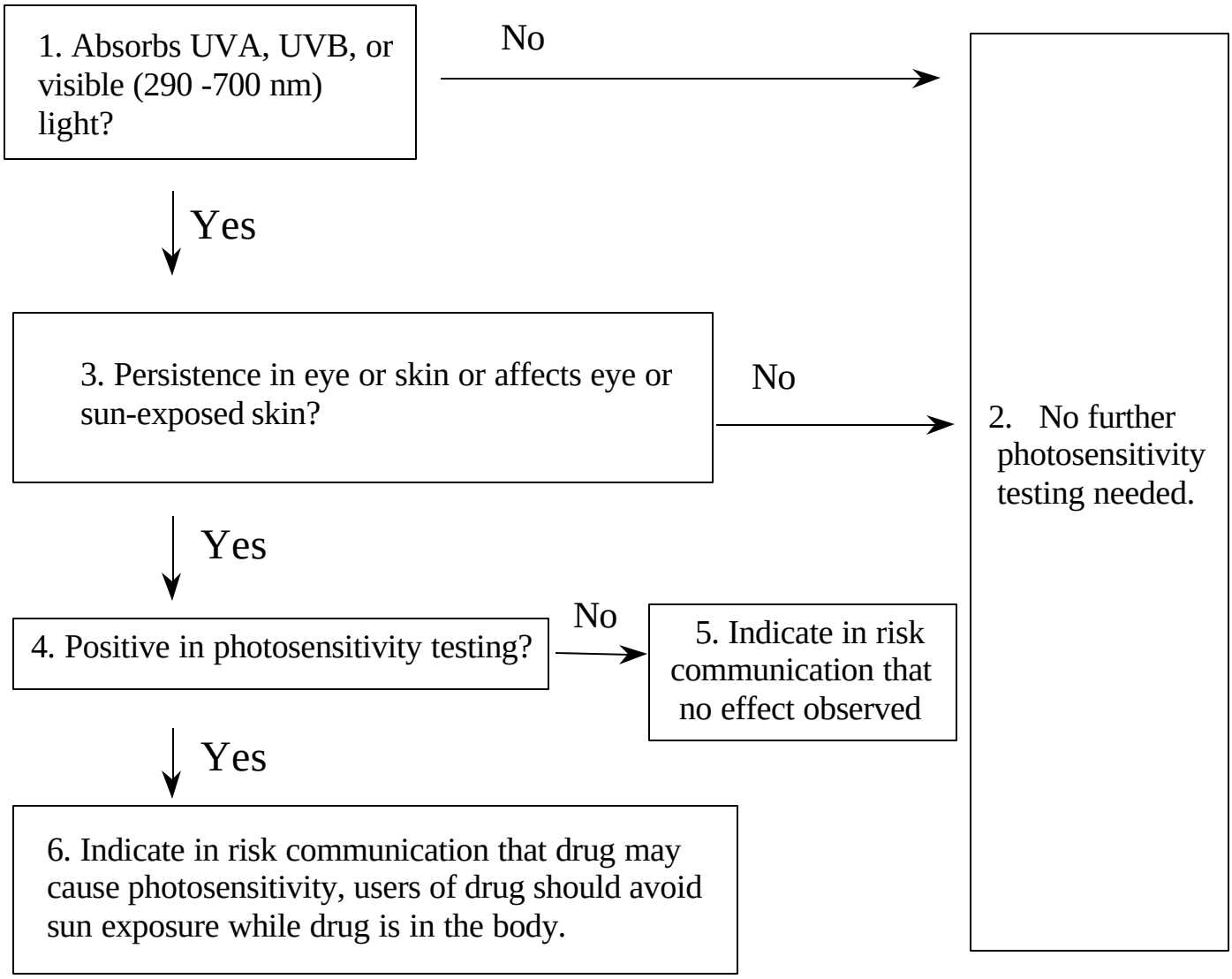
UVA: Ultraviolet radiation A (wavelengths between 320-400 nm)

UVB: Ultraviolet radiation B (wavelengths between 290-320 nm)

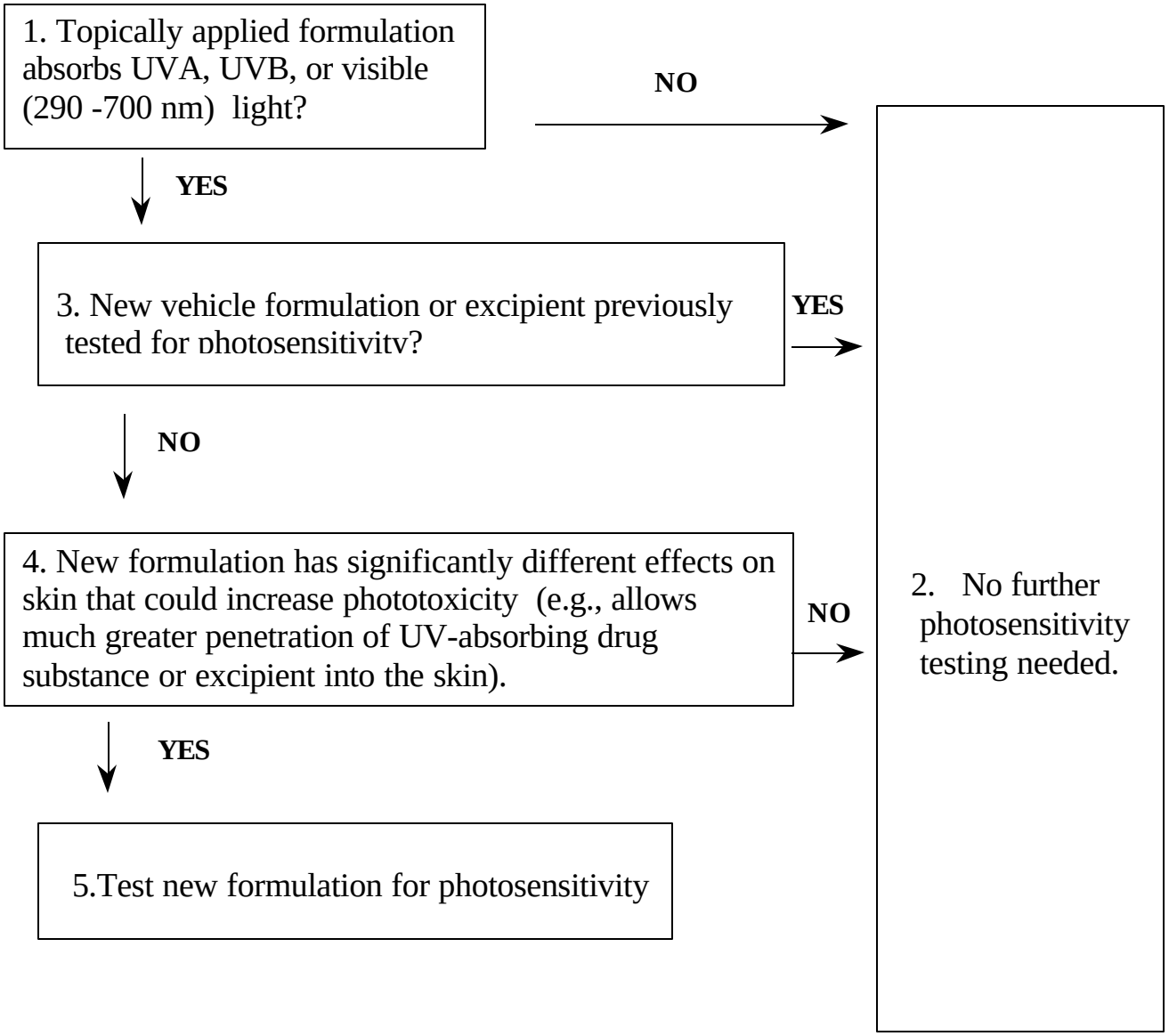
UVC: Ultraviolet radiation C (wavelengths less than 290 nm)

ATTACHMENT

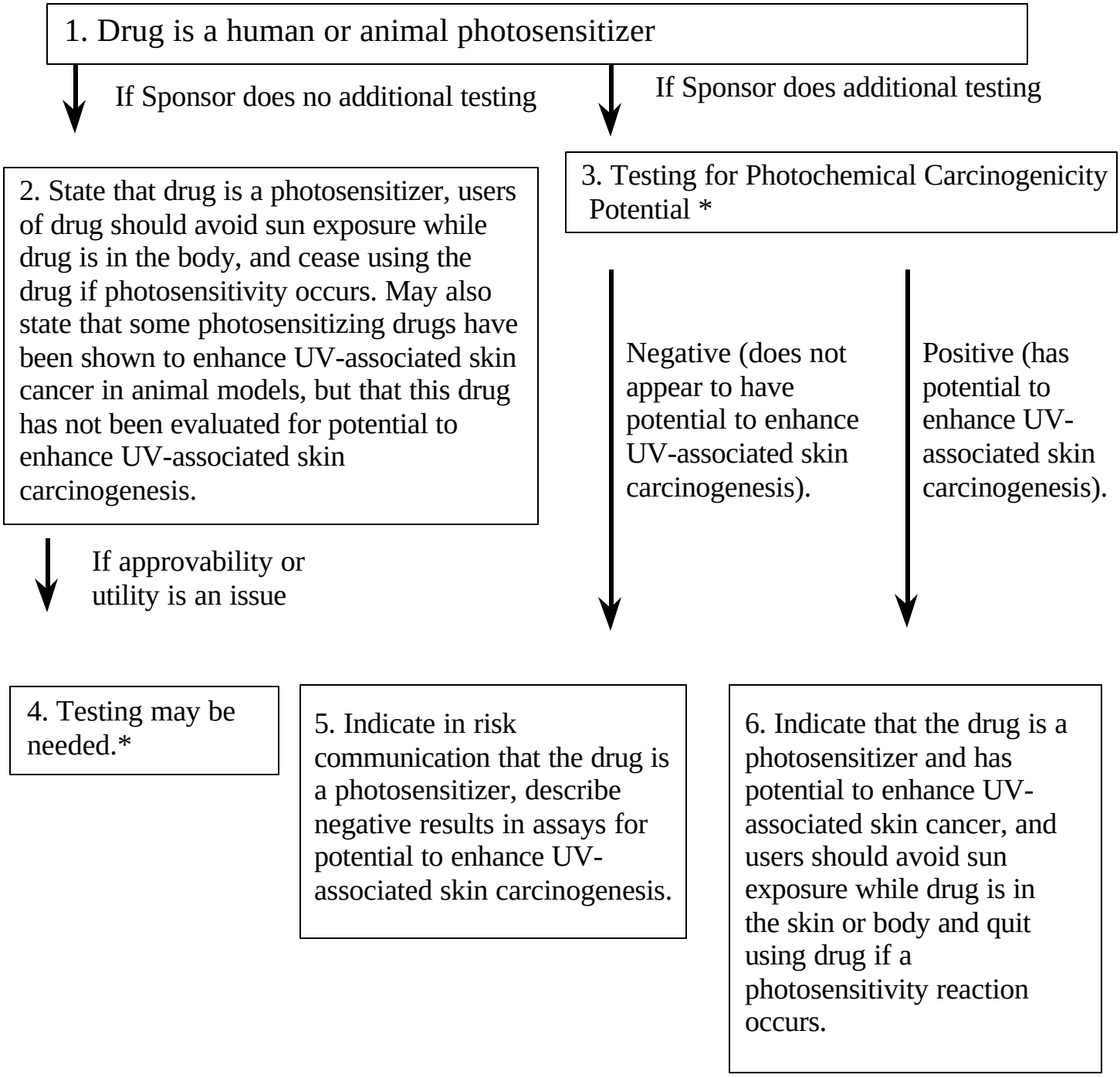
A1. DECISION TREE TO IDENTIFY THE NEED FOR SHORT-TERM PHOTOSENSITIVITY TESTING



A2. DECISION TREE TO IDENTIFY THE NEED FOR TESTING AFTER REFORMULATION OF A TOPICAL PREPARATION

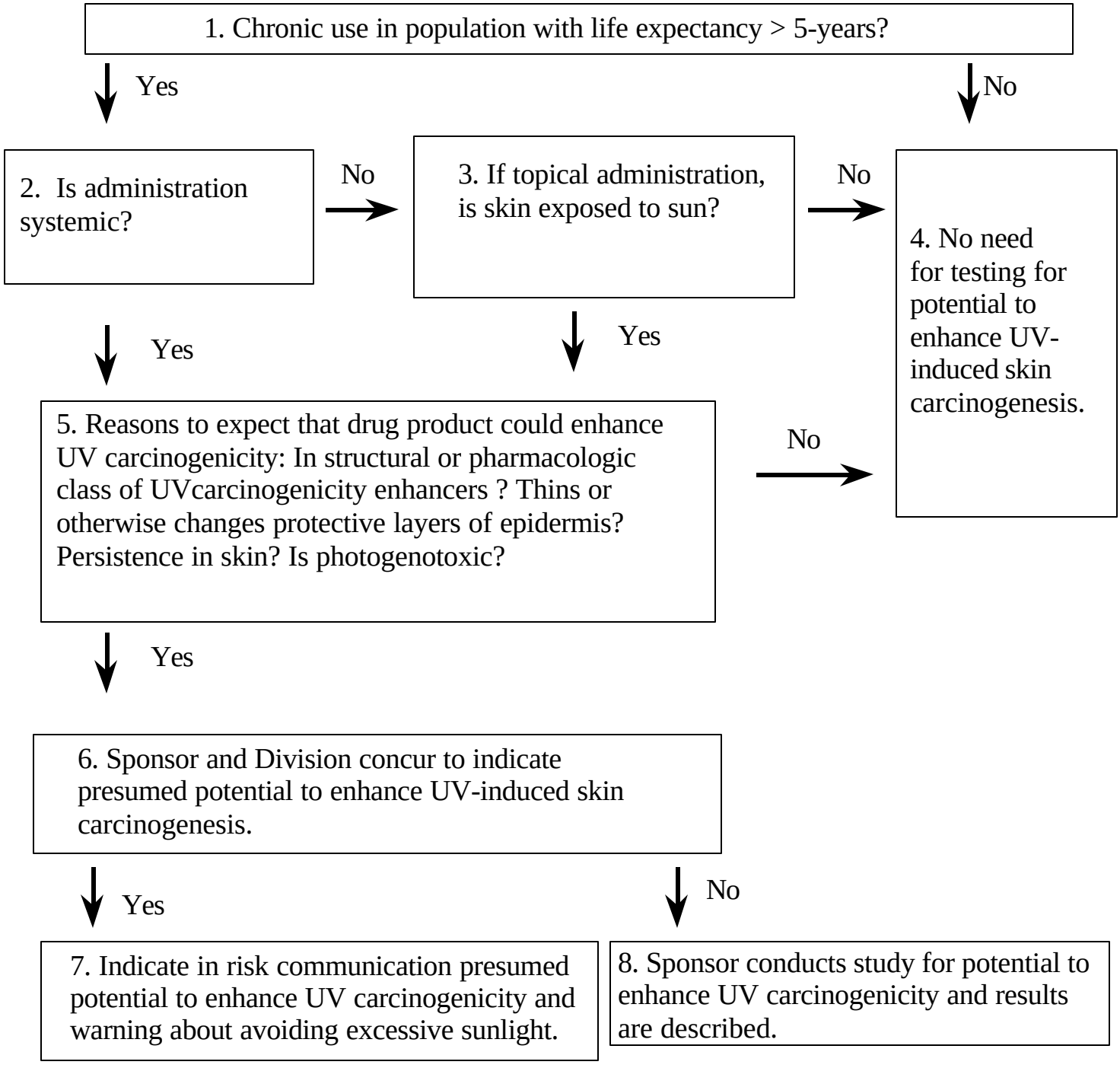


B. TESTING FOR THE PHOTOCHEMICAL CARCINOGENICITY POTENTIAL* OF PHOTOREACTIVE PHOTOSENSITIZING DRUG PRODUCTS AND LABELING OUTCOMES



* Testing should be in an appropriate model.

C. TESTING OF NONPHOTOSENSITIZING DRUG PRODUCTS FOR POTENTIAL* TO ENHANCE UV-INDUCED SKIN CARCINOGENESIS



*Products specifically intended for use in sunlight should be tested for potential to enhance UV carcinogenicity.